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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/769,144	01/30/2004	Tibor Keler	CDJ-301RCE3	9318

959 7590 03/14/2011

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EXAMINER	
KIM, YUNSOO	
ART UNIT	**PAPER NUMBER**
1644	

MAIL DATE	DELIVERY MODE
03/14/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/769,144	KELER ET AL.	
	Examiner	Art Unit	
	YUNSOO KIM	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-36,39-41,44,48-52,55,56 and 59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-36,39-41,44,48-52,55,56 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/14/11,2/11/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 33-36, 39-41, 44, 48-52, 55, 56 and 59 are pending and are under consideration.

2. Applicant's IDS filed on 1/6/11, 1/14/11 and 2/11/11 have been acknowledged.

3. In light of Applicant's amendment filed on 1/6/11, the objections set forth in the office action mailed on 7/7/10 have been withdrawn (see sections 5-6). Claims 41 and 44 as currently amended recite the proper dependency.

4. The following rejection remains.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 33-36, 39-41, 44, 48-52, 55, 56 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/85798 (IDS reference, of record) in view of U.S. Pat. No. 5,869,057 (IDS reference, of record) for the reasons set forth in the office action mailed on 7/7/10.

The '798 publication teaches a method of inducing an immune response by contacting antigen presenting cells (APC), particularly dendritic cells (DC), with a composition comprising a molecular conjugate (i.e. complex) of a human monoclonal antibody conjugated to a tumor antigen (p. 5-6, 54-55, claims, 33-42, see entire document, particularly the abstract, pages 2, 5-6, 8, 43, 53-57, and claims 33-42) and methods of inducing immune response by administering the composition comprising the molecular conjugate.

The '798 publication also discloses a monoclonal antibody that binds to the macrophage mannose receptor present on DC, and that such antibodies are desirable for practicing the methods disclosed in the '798 publication (see particularly claims 5 and 34). The conjugates of the '798 publication are disclosed as being formed in various ways, including as fusion proteins produced recombinantly (see particularly pages 5, 44, 54, 55). The antibodies used in such conjugates are disclosed as being human, humanized, chimeric and antigen binding fragments such as Fab and scFv (see particularly pages 36 and 39). Notably, the '798 publication teaches the antibody comprising SEQ ID NOs:4 and 8 recited in the instant claims (see particularly Fig. 13, B11 V_L and B11 V_H proteins). Note that the recited SEQ ID NOs:4 and 8 encompass the CDRs identified as in SEQ ID NOs:13-18 in claim 41 of the instant application and claim 41 is included in this rejection.

Moreover, the '798 publication teaches in vivo and ex vivo internalization of the antibody-antigen by APC which leads to the generation of immune responses mediated by MHC-I/II complexes including the elicitation of CD4+, CD8+ and cytotoxic T cells (see particularly pages 5-6, 26, 35, 36, 38-41, 56-58 and claims 5, 16, 23-27, 32, 38-42).

The disclosure of the '798 publication differs from the instant claimed invention in that it does not teach the use of βhCG as an antigen as is currently recited in claims 33, 50 and 59 of the instant application.

The '057 patent teaches the use of βhCG as an antigen that is detectable on 74 different cancer cell lines (see entire document, particularly col. 3, lines 40-50, and col. 5, lines 32-60). The '057

patent further teaches that the βhCG is expressed and is detectable on the surface of tumor cells and could be used in immunization against βhCG and an antimetastasis treatment. Given that the '057 patent teaches the preclusion of additional adjvuant (col. 11, lines 47-64), it meets the limitations of the currently amended claims of 33, 50 and 59.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ βhCG as a tumor antigen as taught by the '057 patent in the molecular conjugate comprising a human monoclonal antibody that binds to dendritic cells and immunostimulatory cytokine taught by the '798 publication to practice the claimed method.

One of ordinary skill in the art would have been motivated to do so because of the well known characteristics of βhCG as a tumor antigen in treatment and its availability on many known tumor cells as taught by the '057 patent (col. 3, col. 5, in particular).

From the teachings of references, it would have been obvious to one of ordinary skill in the art to combine the teachings of the references and there would have been a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time of invention was made, as evidenced by references, especially in the absence of evidence to the contrary.

Applicants' arguments filed on 1/6/11 have been fully considered but they were not persuasive.

Applicant has asserted that the combination of the references does not result in the claimed invention. Applicant has asserted that the βhCG in the claimed invention and the prior art are different and βhCG encompassed by the claimed invention is not limited to the particular sequence. Applicant has further asserted that the previously submitted and considered Lund et al. reference suggests that the βhCG requires adjuvant as well as the prior art teaches the adjuvants are required to effectively produce βhCG vaccines (p.7-11 of response filed on 1/6/11). Moreover, Applicant has asserted that the βhCG-based vaccine requires an adjuvant and Applicant is the first to develop the βhCG-based vaccine without any adjuvant.

However, Applicant's assertion in that the βhCG in the claimed invention and the prior art are different is misleading. As both prior art and Applicant aware, the βhCG refers to the beta subunit of human chorionic gonatotropin and it is derived from the SEQ ID No:20 (p.12 of the instant specification). Unless Applicant recites specific features that differentiate the claimed βhCG from the prior art, the prior art βhCG reads on the claimed invention.

Further, as previously discussed based on the references submitted by Applicant (Gupta et al., Lund et al., Dalum et al., and Triozzi et al. references), the prior art recognizes addition of adjuvant for βhCG for more potent immune response but some fragment of the βhCG does not require adjuvant. As discussed previously, the βhCG used in the Triozzi et al. reference is from carboxyl end of hCG (the first 37 amino acids). Lund et al. reference (also provided by Applicant) clearly discloses that the 37 amino acids from carboxyl terminus of βhCG requires immunogenic carrier protein while the holo- βhCG hormone does not require any adjuvant. Moreover, Lund et al. teach that the purified βhCG in the absence of carrier protein elicits immune response (p. 71, under T cell epitope). Based on the references provided by Applicant, only carboxyl end of hCG may elicit more potent immune response in the presence of carrier protein. The claimed βhCG is derived from SEQ ID NO:20 as is defined by the specification of the instant application in p.12. The claimed βhCG is outside of the carboxyl terminus (e.g. 1-37 amino acids) that is corresponding 61-69 of the entire hCG. Thus, Applicant's assertion based on the segment of hCG that is not recited in the claimed invention is irrelevant. Applicant has further asserted that the CTP (corresponding 113-145 amino acid of βhCG) region of βhCG (p. 8 -9 of the response filed on 1/6/11) does not induce T cell response in the absence of carrier. As discussed above, the CTP region does not correspond to the claimed βhCG. Without differentiating specific structure features of the claimed βhCG from the prior art βhCG, the claimed βhCG reads on any fragments or variants of the βhCG (p. 12 of the specification).

Further, Applicant's assertion based on the requirement of additional protein carrier molecule when the βhCG molecule is used is misleading. Applicant has asserted that Gupta et al., Triozzi et al., Dalum et al. and Lund et al. demonstrated that the protein carrier or helper T cell epitopes

is required to render this self antigen to be immunogenic. As discussed above, the carboxyl end of hCG is different from the claimed βhCG.

Applicant has cited the excerpts from the previous response and the Lund et al. reference.

> Moreover, the Examiner characterizes Lund *et al.* (Reviews of Reproduction 3:71-76
> (1998)) as follows:
>
> Lund et al reference (also provided by Applicant) clearly discloses that the 37 amino acids from the carboxyl terminus of 13hCG requires immunogenic carrier protein while the *holo-flhCG* enzyme does not require any adjuvant (emphasis added).
>
> However, the actual quote from Lurid *et al.* referred to by the Examiner reads as follows:
>
> Triozzi et al (1997) immunized non-HLA-matched human subjects with the 37 amino acid CTP covalently linked to DT. Subsequently, T cell proliferative responses could be obtained after stimulation in vitro with *hCG holo-hormone,* but not with the CTP in the absence of a carrier (emphasis added).

However, the quotes from the Lund et al. state the following:

> A prerequisite from the induction of the immune response against a protein antigen is that the antigen is taken up by specialized antigen presenting cells (APC) such as dendritic cells after proteolytic degradation, selected peptide fragments (T cell epitopes) are expressed on the cell surface of the APC in association with major histocompatibility complex (MHC) encoded molecules. When the MHC-peptide complexes are recognized by antigen specific T cell receptors on CD4+ helper T cells, the cells become activated and begin synthesis and secreetion of cytokines that help to stimulate B cells to secrete antigen specific antibodies. Small molecules containing no suitable T cell epitopes can be made immunogenic by covalently attaching larger carrier proteins such as tetanus toxide or diphtheria toxoid. Purified hCG in the absence of carrier protein can elicit an antibody response in mice and rabbits implying that one or both subunits contain appropriate helper T cell epitopes...(p. 71, right hand col).

Therefore, the prior art recognizes the induction of immune response without a carrier protein as long as the antigenic protein contains some forms of T cell epitope. As discussed above and previously, molecular conjugate taught by the '798 publication binds macrophage mannose receptor on dendritic cells is conjugated to a tumor antigen and this conjugate binds autoantigen

(p. 36). Given that this conjugate leads in vivo and ex vivo internalization of the antibody-antigen by APC which leads to the generation of immune responses mediated by MHC-I/II complexes including the elicitation of CD4+, CD8+ and cytotoxic T cells (see particularly pages 5-6, 26, 35, 36, 38-41, 56-58 and claims 5, 16, 23-27, 32, 38-42). Thus, the prior art molecular conjugate in fact acts as a protein carrier and successfully induces T cell mediated immune responses. Given that the prior art molecular conjugate acts as a protein carrier and induces T cell mediated response, the prior art molecular conjugate would be immunogenic when it is conjugated to βhCG.

Note that since the vaccine compositions of the '057 patent are useful because they induce an immune response, and because the '798 publication discloses methods by which immune responses are increased by specifically targeting antigens to the APC which are responsible for initiating the immune response, a person of ordinary skill in the art would be motivated to use the constructs of the '057 patent in the molecular conjugate of the '798 publication in order to induce a stronger immune response by virtue of increasing antigen presentation.

As discussed previously, methods which employ a conjugate of antigen and an antibody against MMR to form a molecular conjugate which directly targets the human MMR on APC and induces an immune response mediated by both CD4+ and CD8+ T cells were taught by the '798 publication. The CTL response mediated by CD4+ and CD8+ T cells and MHC-I/II complexes are taught throughout the '798 publication and such immune response are achieved by the molecular conjugation of monoclonal antibody that binds to the macrophage mannose receptor on APC and a tumor antigen. Indeed, beginning on page 54, the '798 publication discloses:

> In another embodiment, the methods and compositions of the invention can be used to modulate an immune response in a subject towards an antigen. The human anti-dendritic cell antibodies of the invention can be used to target an antigen to a dendritic cell and thereby modulate antigen presentation and processing, such that an immune response to the antigen is induced. The antigen can be a tumor antigen, or an antigen from a pathogen, e.g., a microbial pathogen. The pathogen can be a virus (e.g., HIV), a bacterium, a fungus, or a parasite. The antigen can also be a component of an amyloid deposit in a

patient, such as a patient suffering from Alzheimer's disease and the antigen is Aβ peptide.

For example, a molecular complex comprising at least one binding specificity for a component on the surface of a dendritic cell linked to an antigen, wherein binding of the complex to the dendritic cell mediates internalization of the molecular complex, can be administered to a subject to induce or enhance an immune response against the antigen. The immune response generated against the antigen includes antibodies that bind to the antigen and T cells that bind to the antigen as a component of an MHC-I or MHC-II complex. Accordingly, the human anti-dendritic cell antibodies of the invention can also be used to mediate dendritic cell-targeted immunization of a subject. For example, a subject can be immunized with a molecular complex comprising at least one binding specificity for a component on the surface of a dendritic cell linked to an antigen, wherein binding of the complex to the dendritic cell mediates internalization of the molecular complex, and, for example, enhances processing and presentation of the antigen.

Further, the '798 publication states:

"bispecific and multispecific molecules of the invention comprises a binding specificity for an antigen on a target cell, e.g. a tumor cell antigen, a microbial antigen, a viral antigen or an autoantigen and a second binding specificity for dendritic cells" (p. 36, lines 22-25) and

"Thus, the antibodies of the invention can be used to stimulate the immune response to pathogens, toxins and self-antigens" (p.55, lines 17-18).

Thus, it is clear that the '798 publication discloses methods whereby an tumor antigen is targeted for efficient uptake and presentation on MHC class I and II molecules via conjugation of the tumor antigen to an dendritic-cell specific antibody. Note that the '057 patent is provided to show the motivation to select the βhCG as a tumor antigen because it is expressed and detectable on the surface of many tumor cells. The '057 patent further discloses that βhCG is to be used for immunization and as an antimetastasis treatment (col. 3, lines 40-50, col. 5, lines 32-60).

Therefore, a person of ordinary skill in the art would have been motivated to use βhCG as the tumor antigen in the methods of generating an anti-tumor antigen immune response that are disclosed in the '798 publication since the '057 patent discloses that βhCG is a tumor antigen that is to be used in vaccines to stimulate an immune response to the tumor antigen, and that βhCG is

a particularly desirable tumor antigen to target because it is expressed on a wide variety of different tumors.

Further, the '057 patent discloses generically that βhCG is a tumor antigen. Tumor antigens are self antigens, and as such they all display some degree of "self-tolerance". Note that the '798 publication explicitly states that tumor antigens are to be used. Given that the '798 publication teaches that the molecular conjugate that is capable of inducing T cell response and the '057 patent provides motivation to select βhCG as a tumor antigen, the combination of references provides reasonable expectation of success and predictability to support a conclusion of nonobviousness. See MPEP 2143.02.

Furthermore, Applicant has asserted that the claimed composition requires no adjuvant or immunostimulatory agent. However, the specification of the instant application defines adjuvant to include preservatives, wetting agents, emulsifying agent and dispersing agent (p. 30). The exemplary preservatives, wetting agents or emulsifying agent includes polyols, surfactants and the like (p. 30, lines 11-25). Given that the surfactant such as Tween 20 acts as an adjuvant in the vaccine art, the claimed composition does not preclude substances which have multiple properties. Even if the claimed composition precludes any means of adjuvant in the composition, at any stages of treatment, the claimed invention is still obvious over the combination of the prior art. The '057 patent states (col. 11, lines 47-64):

> My invention offers four primary advantages over prior art. ...
> Second, my invention precludes the need for additional adjuvants such as muramyl dipeptide in the final vaccine formulation (lines 54-55).

Therefore, the prior art recognizes preclusion of additional adjuvant if self and non-self recognition is established using the antigen such as βhCG and the presence of T cell immune response inducing protein carrier is achieved by the '798 publication. The combination of the references remains obvious and thus rejection is maintained.

7. No claims are allowable.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to YUNSOO KIM whose telephone number is (571)272-3176. The examiner can normally be reached on M-F, 9-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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